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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/625,073	07/22/2003	Mark I. Greene	UPN-5191	9446

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EXAMINER	
JAVANMARD, SAHAR	

ART UNIT	PAPER NUMBER
1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/625,073	GREENE ET AL.	
	Examiner	Art Unit	
	SAHAR JAVANMARD	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-5* is/are pending in the application.

4a) Of the above claim(s) *6-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

This Office Action is in response to applicant's arguments filed on 3/4/08. Claim(s) 1 and 3-5 are pending and are examined herein.

Response to Arguments

Applicant's arguments with respect to the 112 1st rejection of claims 1 and 3-5 as it applies to enablement were not found persuasive and the rejection is hereby maintained. Even though a working example is not required in order to obtain a patent, the specification does not provide sufficient guidance to enable one of ordinary skill in the art to reproduce the invention without undue experimentation. The rejection is maintained and has been restated below for Applicant's convenience.

Applicant's arguments with respect to the 102(b) rejection of Boyle (EP0784093) have been fully considered but not found persuasive as Applicant is now arguing based on amended claims. Since Applicant has amended the claims, said rejection is hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 are rejected under 35 U.S.C. 1 12, first paragraph, because the specification, while being enabling for a method of treating patients who have diseases characterized by bone loss comprising administering an amount of TRANCE/RANK inhibitors, wherein said inhibitors are selected from known TRANCE/RANK inhibitors as described in the prior art, does not reasonably provide enablement for a method of treating patients who have diseases characterized by bone loss comprising administering an amount of TRANCE/RANK inhibitors, wherein said inhibitors are selected from Formula I (and in particular the species IA). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the ad; (4) the predictability or unpredictability of the ad; (5) the breadth of the claims', (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

The Nature of the Invention:

The rejected claims are drawn to a method of treating patients who have diseases characterized by bone loss comprising administering an amount of TRANCE/RANK inhibitors effective to inhibit osteoclastogenesis and/or osteoclast function.

Breadth of the Claims:

The breadth of the claims are exceptionally broad encompassing a method of treating patients who have diseases characterized by bone loss comprising administering to said patient any TRANCE/RANK inhibitor effective to inhibit osteoclastogenesis and/or osteoclast function.

Guidance of the Specification:

The guidance of the specification as to a method of treating patients who have diseases characterized by bone loss comprising administering an amount of TRANCE/RANK inhibitors effective to inhibit osteoclastogenesis and/or osteoclast function is limited. On pages 40-55 of the specification a series of chemical structures covering Formulas I-XII are detailed. On pages 37-39

Compounds possessing other activities are not described in an enabling fashion.

Working Examples:

The applicant provides two working examples. Example I on pages 37-38 of the

specification, details the use of therapeutic peptidomimetics that interfere with the TNF/TNF receptor interaction as developed by Takasaki et al. A particular peptidomimetic (WP9QY) that inhibits osteoclastogenesis by acting as a TRANCE/RANK inhibitor is disclosed in an in vitro assay. No other compounds are described.

Example 2 describes the identification of the formation of osteoclasts via an in vitro assay wherein a positive control is osteoprotegerin (OPG). Thus OPG is a TRANCE/RANK inhibitor. The in vitro assay is based upon Nicholson et al. (see page 39 of specification).

State/predictability of the Art:

The state of the art regarding a method of treating patients who have diseases characterized by bone loss comprising administering an amount of TRANCE/RANK inhibitors effective to inhibit osteoclastogenesis and/or osteoclast function is limited.

In a paper by Simonet et al. (Osteoprotegerin: A Novel Secreted Protein Involved in the Regulation of Bone Density, Cell, 1997, vol. 89, pp. 309-319), a novel secreted glycoprotein from the TNF superfamily was identified and called osteoprotegerin (OPG). In vivo, hepatic expression of OPG in transgenic mice results in a profound yet non-lethal ostepetrosis, coincident with a decrease in later stages of osteoclast differentiation. The same effect was seen when OPG was administered to normal mice. In vitro OPG blocked osteoclastogenesis in a dose-dependent manner. Simonet et al. demonstrate that OPG can act as a soluble factor in the regulation of bone mass and

imply a utility in the treatment of osteoporosis associated with increased osteoclast activity (see summary page 309).

In EP0784093, Boyle et al. describe a secreted polypeptide, termed osteoprotegerin, which is a member of the TNF superfamily, involved in the regulation of bone metabolism (see abstract). On page 3, Boyle et al. describe that methods of treating bone diseases such as osteoporosis, hypercalcemia, Paget's disease of bone, and bone loss due to rheumatoid arthritis or osteomyelitis are possible by administration of the polypeptides and/or via anti-sense or gene therapy. Pharmaceutical compositions comprising OPG nucleic acids and polypeptides are also encompassed.

Mbalaviele discloses, in the abstract of US Patent No. 6239157, a method of inhibiting the differentiation of CD34+ cells into osteoclasts by treating the cells with a peroxisome proliferator-activted receptor-γ, (PPARγ) agonist. In col. 1 lines 35-55, Mbalaviele teaches that there is provided a process for treating osteoporosis by administering an amount of a PPARy agonist. In col. 2 lines 60-68, Mbalaviele teaches that suitable PPARγ, agonists include ciglitazone, pioglitazone, troglitazone, 15-deoxy-$\Delta^{12,14}$-prostaglandin-J2 and indomethacin.

Baker et al. teach, the abstract of US Patent No. 6171860, antisense compounds and compositions and methods of using such for inhibiting the expression of RANK. In col. 2 lines 9-30, Baker et al. teach that RANK is essential to signaling pathways involved in bone morphogenesis, specifically the process of osteoclast differentiation.

Thus the state of the art is limited primarily to therapeutic polypeptides (OPG) and anti-sense compounds and compositions (directed toward inhibition of RANK

expression) for the treatment of diseases characterized by bone loss comprising administering an amount of TRANCE/RANK inhibitors effective to inhibit osteoclastogenesis and/or osteoclast function. PPAR? agonists while inhibiting osteoclastogenesis, are not clearly demonstrated to act through the inhibition of TRANCE/RANK.

No small molecules useful for the treatment of diseases characterized by bone loss comprising administering an amount of TRANCE/RANK inhibitors effective to inhibit osteoclastogenesis and/or osteoclast function have been found in the prior art.

The Quantity of Experimentation Necessary:

The instant claims read on a method of treating patients who have diseases characterized by bone loss comprising administering to said patient TRANCE/RANK inhibitors of formula I effective to inhibit osteoclastogenesis and/or osteoclast function. As discussed above, the specification fails to provide sufficient support for agents other than peptidomimetic (WPgQY) and OPG. The prior art provides support for anti-sense agents useful in the inhibition of RANK expression. Applicant fails to provide information sufficient to practice the claimed invention, absent undue experimentation (i.e. testing all small molecule agents described in methods of treating patients having diseases characterized by bone loss, further testing all small molecule agents described in TRANCE/RANK inhibition assays and in osteoclastogenesis inhibition assays and/or osteoclast function assays). *Genetech*, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful

conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable." Accordingly the claims are evaluated as being drawn to a method of treating patients who have diseases characterized by bone loss comprising administering an amount of TRANCE/RANK inhibitors of formula I effective to inhibit osteoclastogenesis and/or osteoclast function, wherein the TRANCE/RANK inhibitor is the peptidomimetic WP9QY, OPG polypeptide(s), and/or the anti-sense agents described by Baker et al.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4 and 5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is not clear from the claim what the structure of formula I is. The rejection can be overcome by inserting the structure in the claim.

Claim 3 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The instant claim is dependent on cancelled claim 2. For sake of advancing prosecution, Examiner assumed that claim 3 is dependent on claim 1.

Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant

regards as the invention. It is not clear what the group consisting of I-A, I-B, I-C, I-D, I-E, I-F, I-G, I-H, and I-I is supposed to exactly mean.

Conclusion

Claims 1 and 3-5 are not allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAHAR JAVANMARD whose telephone number is (571) 270-3280. The examiner can normally be reached on 8 AM-5 PM MON-FRI (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/S. J./

Examiner, Art Unit 1617

/SREENI PADMANABHAN/
Supervisory Patent Examiner, Art Unit 1617